REMARKS

A final Office Action was mailed August 16, 2011. Claims 1, 4, 5, 7- 21, 23, and 24 are pending in the application and were rejected in the Office Action. Applicant respectfully requests reconsideration of the Application in view of the remarks below.

Applicant appreciates the Examiner's withdrawal of the 35 U.S.C. 112, second paragraph rejection of claims 1, 7, 10-11, and 21 following Applicant's last amendment. Applicant also appreciates the Examiner's withdrawal of the duplicate, obviousness-type double patenting rejection.

The claims of the present application relate to an unexpected improvement in bioavailability of ospemifene when consumed at or near the time of foodstuff.

I. THE FIRST REJECTION UNDER 35 U.S.C. §103(a) IS IMPROPER BECAUSE THE CITED REFERENCES FAIL TO TEACH ALL LIMITATIONS OF THE CLAIMS

Claims 1, 4, 5, 7, 10, 11, 14, and 18-20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over DeGregorio et al. (US 5,750,576, hereinafter DeGregorio) in view of Anttila (1997) and further in view of Guidance for Industry (2002, hereinafter Guidance document).

M.P.E.P. 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The 35 U.S.C. § 103(a) obviousness rejection of claims 1, 4, 5, 7, 10, 11, 14, and 18-20 is improper because the cited references fail to disclose all of the claimed

limitations. In addition, they fail to provide a reasonable expectation of success because the food effects on ospemifene bioavailability are unpredictable.

The Office Action identifies DeGregorio as the primary reference. The Office Action indicates that DeGregorio discloses ospemifene as a pharmaceutically acceptable salt in an orally administered from in varying dosage amounts of 5-100 mg/day for the treatment of osteoporosis.

The Office Action acknowledges that DeGregorio fails to disclose all of the limitations of any of the pending claims in two ways. First, the Office Action acknowledges that DeGregorio fails to teach the administration of ospemifene with intake of foodstuff (taken shortly before, during, or after administration). (Aug. 16, 2011, Office Action at p. 4, 1st ¶.) Second, the Office Action also acknowledges that DeGregorio fails to teach the dosage amounts recited in dependent claims 10-11, 19-20.[1] (*Id.* at p. 3, 4th ¶- p. 4 1st ¶.)

Given the clear shortcoming of DeGregorio, the Office Action cites Anttila purportedly to show that structurally similar compounds are known in the art to be administered with or without food. (*Id.* at p. 4, 2nd ¶.) Specifically, the Office Action indicates that Anttila teaches administration of 60 mg/day of a structurally similar compound toremifene during or after a meal. (*Id.* at p. 4, 3rd ¶).

A. Anttila fails to teach an improvement in bioavailability of toremifene when taken at a meal.

Anttila, however, does not teach that the administration of toremifene results in an *improvement* of bioavailability.

The study reported in Anttila "was designed to determine the effect of food on the bioavailability of toremifene administered orally to healthy volunteers." (Introduction, 2nd ¶.) The study methodology reportedly used twelve, male volunteers. (Methodology, 1st ¶.) Toremifene was administered as a single 60 mg tablet with water after (1) either an overnight fast or (2) after a standard high-fat breakfast consisting of two eggs fried in

[1] Applicant notes that claims 12 and 13 also recite specific dosage limitations even though the Office Action did group these claims with claims 10-11 and 19-20.

butter, two strips of bacon, 60 g of hash brown potatoes, two slices of toast with butter, and 240 ml of whole milk. (*Id.* at 2nd ¶.) Venous bloods samples were taken and measured at various time intervals. (*Id.* at 3rd ¶.) Concentrations of toremifene and its major metabolite (N-demethyltoremifene) were measured. (*Id.*) These parameters were used for the conclusions reported by Anttila.

The conclusions reported by Anttila do not support the obviousness rejection. The reference expressly states that no improvement in bioavailability of toremifene was observed. (Conclusions.) In fact, Anttila reported that the data for toremifene "cogently demonstrate *equivalent* bioavailability of the drug under fed and fasted conditions." (*Id.* emphasis added.) Interestingly, the rate of toremifene absorption from the gastrointestinal tract was decreased by a high-fat meal. (*Id.*) Because the extent of overall toremifene absorption is the same under fed and fasted conditions, however, Anttila concluded that the slower absorption "should not require any dosage modifications." (*Id.*)

From the conclusions in Anttila, one of skill in this art would understand that toremifene bioavailability when taken with foodstuff is unchanged when compared to ingestion by a patient in a fasting state. That Anttila conclusion, therefore, does not teach or suggest an improvement in bioavailability of toremifene when taken with food. Likewise, it cannot suggest or teach an improvement in the bioavailability of ospemifene as recited in the claims.

Applicant provided a Declaration by Dr. Risto Lammintausta filed on April 30, 2010, addressing Anttila as well. The Declaration avers that Anttila fails to show that toremifene bioavailability is improved when administered with food (Lammintausta Declaration at ¶23). The Declaration also establishes that even though ospemifene and toremifene are structural relatives, their pharmacokinetics are significantly different in regard to their elimination rates and metabolism (*Id.* at ¶22). These facts further demonstrate that Anttila cannot be relied upon to support a rejection of Applicant's claims.

B. The Guidance document also does not disclose that drug bioavailability improves when a drug is taken with foodstuff.

The Office Action cited the Guidance document as a tertiary document (an additional secondary reference). It does not, however, teach ospemifene would have improved bioavailability if taken with foodstuff.

The Office Action indicated that The Guidance document teaches "food effect bioavailability" studies are conducted with new drugs shortly after a meal and compared to a fasting condition. (Office Action at p. 5, 1st ¶.) In fact, that is not supported by the reference.

As an initial matter, the U.S. Food and Drug Administration (FDA) produced the Guidance document cited by the Office Action. The document's stated purpose is to provide recommendations to sponsors and applicants planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies in conjunction with investigational, new, and abbreviated drug applications. (P. 1, 1st ¶.) It does not provide information specific to ospemifene, toremifene, or other selective estrogen receptor modulators (SERMs). Moreover, the Guidance document nowhere teaches that food makes drugs more bioavailable as a general rule, either systemically or in the GI tract.

The Guidance document at most teaches that administration of oral drug products with food can alter the dissolution, transit time, and permeability of such drug products in the gastrointestinal tract. The Guidance document does not teach or suggest that food can increase the bioavailability of a drug. In addition, the Guidance document also teaches that food effects on Class II drugs, which ospemifene is a member, are "difficult if not impossible to predict without conducting a fed [bioequivalence] study." (P. 2, last ¶.) Indeed, the "relative direction and magnitude of food effects on formulation" bioavailability underscores why such studies are recommended by the FDA. (*Id.*) In other words, the Guidance document states that food affects oral drug products differently and unpredictably. It also specifically cites

differences between drugs that are highly soluble and highly permeable (Class I drugs) and those which are highly permeable and which have low solubility (Class II drugs).

The MPEP acknowledges that for an obviousness rejection "at least some degree of predictability is required." (M.P.E.P. 2143.02(II).) As reflected in the Guidance document, there is no predictability for class II, III, and IV drugs whether and to what degree food ingestion at near the time of administration of an oral drug will impact the bioavailability of the drug. (P. 2, last ¶.) The Guidance document does not, therefore, teach that the bioavailability of ospemifene when taken at or about the time of food ingestion will result in improved bioavailability.

The express statements made in the Guidance document should not be overlooked. The MPEP acknowledges this requirement: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." (M.P.E.P. 2141.03(IV) *citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (emphasis in original.)

Taking the logic of the actual teachings of the references cited in the Office Action, at best one of skill in this art would have a reasonable expectation that ingesting a structurally similar compound to toremifene would result in no change in overall bioavailability. More consistently, one of skill in this art would not have a reasonable expectation that ingesting structurally similar compounds to toremifene could be predicted.

C. There is no prima facie showing of obviousness.

Applicant remarked previously and repeats that a prima fascia showing of obviousness is not established by the combination of the three references. None of DeGregorio, Anttila, and the Guidance document disclose all of the claim limitations. They do not teach or suggest that administration of ospemifene at or about the time of food ingestion results in improved bioavailability of the drug.

When read carefully, Anttila and the Guidance document demonstrate the unpredictable nature of bioavailability effects of drugs ingested with or near the time of

food consumption. The unpredictable nature of food ingestion with oral drug delivery is expressly acknowledged in the Guidance document. Without more, the Office Action obviousness rejection fails to teach all of the claim limitations and fails to provide any level of predictability upon which a reasonable expectation of improved bioavailability can be found.

The Office Action at page 9 argues that "structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious." This blanket statement is incomplete. As recognized in MPEP, "Homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed 'as a whole.'" (M.P.E.P. 2144.09(II) *citing In re Langer*, 465 F.2d 896 (CCPA 1972).) The Office Action fails to account for the whole teachings of the references.

First, it is recognized in this art that toremifene and ospemifene are SERMs. It is also recognized in this art that SERMs have unpredictable, disparate activities. (*See* Lammintausta Declaration at ¶¶6-17.) Researchers in this art recognize this unpredictability. For example, some have stated "[T]he profile of tissue-specific effects of each SERM is still unpredictable and was based mainly on animal and clinical studies." (*See* Tian-Li Yue, et al. "Selective Estrogen Receptor Modulator Idoxifene Inhibits Smooth Muscle Cell Proliferation, Enhances Reendothelialization, and Inhibits Neointimal Formation In Vivo After Vascular Injury" Circulation, 2000; 102:III-281-III-288 (attached as Exhibit A).) Because it is known in this art that SERM activities are unpredictable, it is inappropriate to presume ospemifene would have the same properties as toremifene.

Second, as articulated above, Anttila did not report that consumption of foods with toremifene resulted in an improvement in bioavailability. It cannot, therefore, be extrapolated that ospemifene would be expected to have improved bioavailability when taken with food. Again from the MPEP, "The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally

similar compounds." (M.P.E.P. 2144.09(V) *citing In re May*, 574 F.2d 1082, (CCPA 1978).) Here, the Guidance document already cited in the Office Action demonstrates the unpredictable properties of bioavailability of Class II, III, and IV drugs which ospemifene is among. (*See* Anttila at p. 2, last ¶.) Dr. Lammintausta's Declaration consistent provides the same proposition. (Declaration at ¶¶6-17.) Moreover, statements by those in the art acknowledge this unpredictability. (Exhibit A.)

Because DeGregorio in view of Anttila and further in view of Guidance for Industry (2002) do not teach or suggest a method to enhance the bioavailability of orally-administered ospemifene, much a less a significant 2-3 fold improvement as demonstrated by Applicant, they do not render obvious the claimed invention. Also, the Guidance document and Applicant's Declaration further establish the inappropriate application of an assumption that structurally similar compounds will have the same properties. Applicant, therefore, respectfully requests that this obviousness rejection be withdrawn.

II. THE SECOND REJECTION UNDER 35 U.S.C. §103(a) IS IMPROPER BECAUSE THE CITED REFERENCES FAIL TO TEACH ALL LIMITATIONS OF THE CLAIMS

Claims 1, 8-9, 12-13, 15-17, and 22-24 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Halonen et al. (US 6,245,819, hereafter Halonen) in view of Anttila (1997) and further in view of Guidance for Industry (2002).

The 35 U.S.C. § 103(a) obviousness rejection of claims 1, 8-9, 12–13, 15-17, and 22-24 is improper because the cited references fail to disclose all of the claimed limitations. In addition, they fail to provide a reasonable expectation of success because the food effects on ospemifene bioavailability are unpredictable.

For this rejection the Office Action identifies Halonen as the primary reference. The Office Action indicates that Halonen discloses ospemifene as an estrogen receptor modulator to women suffering from vaginal symptoms including vaginal dryness. (Office Action at p. 10.)

The Office Action acknowledges that Halonen fails to disclose all of the limitations of any of the pending claims in two ways. First, the Office Action acknowledges that Halonen fails to teach the administration of ospemifene with intake of foodstuff. (*Id.*) Second, the Office Action also acknowledges that Halonen fails to teach inhibition of urogenital atrophy as required in claim 21. (*Id.*)

Like the obviousness rejection relying on DeGregorio as the primary reference, the obviousness rejection relying on Halonen also relies on Anttila purportedly to show that structurally similar compounds are known in the art to be administered with or without food. (*Id.*)

This rejection also relies on the Guidance document. While the statement in the Office Action is unclear, Applicant believes it relies on the Guidance document to show a teaching that "food effect [studies of] bioavailability are conducted with new drugs shortly after a meal and compared to fasting condition." (*Id.* at p. 11, 2nd ¶.)

In response to Applicant's last argument, the Office Action states that Applicant has ignored the rationale underlying the rejection. Moreover, the Office Action states, "Bioavailability is a preamble that does not affect the treatment of skin atrophy." (*Id.* at p. 12, 5th ¶.) In this the Examiner errs.

The MPEP addresses the Examiner's error: "The entire claim must be considered, including the preamble language and the transitional phrase." (M.P.E.P. 2163(II)(A)(1).) Moreover, "[A] claim preamble has the import that the claim as a whole suggests for it." (M.P.E.P. 2111.02 *citing Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995). Enhancing the bioavailability of ospemifene is a necessary limitation in the claims.

For brevity, Applicant will not repeat all of its prior remarks identifying why the obviousness rejection fails to present a prima fascia case. It merits pointing out, however, that the Office Action acknowledged a common deficiency in both primary references, namely that they fail to disclose administration of ospemifene with intake of foodstuff. The reasons identified in Applicant's remarks for the first obviousness rejection are equally applicable here. Anttila does not teach that the administration of

toremifene results in an *improvement* of bioavailability, nor does the Guidance document. Instead, the Guidance document highlights the unpredictable magnitude and direction of food effects on bioavailability of an orally administered drug. (*See* supra.)

Because the combination of Halonen, Anttila, and the Guidance document do not teach or suggest a method to enhance the bioavailability of orally-administered ospemifene or predict the significant 2-3 fold improvement as demonstrated by Applicant, they do not render obvious the claimed invention. Also, the Guidance document and Applicant's Declaration further establish the inappropriate application of an assumption that structurally similar compounds will have the same properties. Applicant, therefore, respectfully requests that this obviousness rejection be withdrawn.

III. THE FIRST REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IS IMPROPER BECAUSE THE CITED CLAIMS AND REFERENCES FAIL TO TEACH ALL LIMITATIONS OF THE CLAIMS

Claims 1, 4-5, 7-21, and 23-24 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,984,665 ("the '665 patent") in view of the Guidance document.

The Office Action asserts that the pending claims are not patentable because both they and the claims 1-3 of the '655 patent recite treating or inhibiting urinary symptoms. (Office Action at p. 13, 4th ¶.) The Office Action acknowledges, however, that the earlier issued patent claims are silent as to teaching the effect of food consumption on drug bioavailability. (*Id.*) To fill that gap, the Office Action relies on the Guidance document for the purported teaching that "food effect bioavailability [studies] are conducted with new drugs shortly after a meal and compared to [a] fasting condition." (*Id.*)

Applicant remarked in response that the Guidance document in combination with the claims fail to teach or suggest enhancing bioavailability. In the Office Action, the Examiner dismissed Applicant's remarks responding that "it is reasonable that

ospemifene is administered within 2 hours after starting the food intake and treatment would occur regardless of bioavailability." (*Id.* at p. 16, 2nd ¶.) The Office Action further states, "Whether enhanced bioavailability is claimed or not does not change the property of the drug when administered." (*Id.*) In this, the Examiner errs.

Applicant's claims relate to a method of *improving* bioavailability of ospemifene. Ospemifene's bioavailability, therefore, is changed as practiced by the claimed invention. It is not an inherent function of the drug to have improved bioavailability. Rather, it is the claimed combination of taking the drug in combination with a foodstuff which results in the 2-3 fold improvement in bioavailability.

The Guidance document alone or in combination with claims 1-3 of the '655 patent fails to predict or suggest an improvement in bioavailability of ospemifene. Rather, the Guidance document teaches that there is uncertainty in what manner orally administration drugs will affect the bioavailability of the drug. The Guidance document explains that food effects on Class II drugs, of which ospemifene is a member, are "difficult if not impossible to predict without conducting a fed [bioequivalence] study." (P. 2, last ¶.) Indeed, the "relative direction and magnitude of food effects on formulation" bioavailability is unpredictable. As such, Applicant respectfully requests that the obviousness-type double patenting rejection be withdrawn.

IV. THE SECOND REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IS IMPROPER BECAUSE THE CITED CLAIMS AND REFERENCES FAIL TO TEACH ALL LIMITATIONS OF THE CLAIMS

Claims 1, 4-5, 7-21, and 23-24 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,245,819 ("the '819 patent") in view of the Guidance document.[2]

[2] Applicant notes that the second obviousness-type double patenting rejection was applied to claims 1, 4-5, 7-21, and 23-24. The remarks in the Office Action, however, were only applied to claims 8 and 15. Applicant believes the Examiner intended to apply the rejection to the broader set of claims and not just claims 8 and 15. Clarification is respectfully requested.

The Office Action indicates that instant claims 8 and 15 are drawn to a method of treating symptoms related to skin atrophy, epithelial or mucosal atrophy in women. (Office Action at p. 16, 4th ¶.) The Office Action acknowledges that the cited patent claims fail to address enhancing bioavailability. (*Id.*) To fill that deficiency, the Office Action reasons that the issued claimed methods of treatment would inherently treat urogenital atrophy as evidenced by the '665 patent specification. (*Id.*) And, like the first obviousness-type double patenting rejection, the Office Action improperly concludes: "Whether enhanced bioavailability is claimed or not does not change the property of the drug when administered." (*Id.* at p. 17, 1st ¶.)

The Guidance document in combination with the earlier issued claims fail to teach or suggest enhancing bioavailability. In the Office Action, the Examiner dismissed Applicant's prior remarks responding that "it is reasonable that ospemifene is administered within 2 hours after starting the food intake." (*Id.* at 3rd ¶.) Apparently, this rejection is also premised on the reasoning for the first obviousness-type double patenting rejection which stated: "Whether enhanced bioavailability is claimed or not does not change the property of the drug when administered." (*Id.* at p. 16, 2nd ¶.) Again, the Examiner errs.

Applicant's claims relate to a method of *improving* bioavailability of ospemifene. Ospemifene's bioavailability is changed as practiced by the claimed invention. It is not an inherent function of the drug to have improved bioavailability. Rather, it is the claimed combination of taking the drug in combination with a foodstuff which results in the 2-3 fold improvement in bioavailability.

The Guidance document alone or in combination with claims 1-3 of the '819 patent fail to predict or suggest an improvement in ospemifene bioavailability. The Guidance document teaches that there is uncertainty in what manner orally administration drugs will affect the bioavailability of the drug. The Guidance document explains that food effects on Class II drugs, of which ospemifene is a member, are "difficult if not impossible to predict without conducting a fed [bioequivalence] study." (P. 2, last ¶.) Indeed, the "relative direction and magnitude of food effects on formulation" bioavailability is unpredictable. Thus, the cited combination would not inherently

disclose or suggest an improved bioavailability of ospemifene when treating skin atrophy, epithelial or mucosal atrophy. Applicant respectfully requests that the obviousness-type double patenting rejection be withdrawn.

V. APPLICANT PROVIDED EVIDENCE OF SURPRISING RESULTS SUPPORTING A FINDING OF NONOBVIOUSNESS

Without acquiescing that a prima fascia obviousness case has been made in the Office Action, it is noteworthy that Applicant's specification provided data showing the surprising observation of improved ospemifene bioavailability. In fact, the data shows that that ospemifene bioavailability improves two- to three-fold when taken just before during, or after food ingestion. This constitutes an unexpected result and is evidence of nonobviousness.

Two clinical studies were carried out using healthy male subjects. (Application at ¶29.) In the first study, Applicant compared ospemifene bioavailability taken during a fasting state was compared to ospemifene bioavailability taken with a high-fat breakfast (860 kcal, Study A). (*Id.*) In the second study, Applicant compared ospemifene bioavailability taken with a high-fat breakfast with ospemifene bioavailability taken with a low caloric breakfast (300 kcal, Study B). (*Id.*)

In the high-fat breakfast study (Study A), ospemifene was administered as a single 60 mg tablet after (1) either an overnight fast or (2) after a standard high-fat breakfast consisting of two eggs fried in butter (50 g), two strips of bacon (34 g), 60 g of hash brown potatoes, two slices of toast with butter (50 g), and 240 ml of whole milk. (*Id.* at ¶30.) Blood samples were taken and measured at various intervals for 72 hours. (*Id.*) Concentrations of ospemifene and its major metabolite (4-hydroxy-ospemifene) were measured. (*Id.* at ¶36.) These parameters are similar to those reported in the study by Anttila. (*See supra.*)

The observations from Study A are shown in Figure 1 which displays the mean serum concentration of ospemifene versus time following administration of ospemifene. (Application at ¶36; Figure 1.) Open circles represent ospemifene administered to

fasting patients. (*Id.*) Filled circles represent ospemifene administered to patients with a high-fat breakfast. (*Id.*) These results show that ospemifene bioavailability was enhanced by concomitant ingestion of ospemifene and a high-fat meal. (*Id.*)

Observations from both Study A and Study B are shown in Figures 2 and 3. (Application at ¶43; Figures 2 and 3.) In Figure 2, open circles represent ospemifene administered to fasting patients, filled circles represent ospemifene administered to patients with a high-fat breakfast, and stars represent ospemifene administered to patients with a low-calorie, low-fat meal. (*Id.*) Similar information is provided in Figure 3 except that the analyte measured is 4-hydroxy-ospemifene, a major metabolite of ospemifene. (*Id.*) These results show that ospemifene bioavailability was enhanced by concomitant ingestion of ospemifene and a meal, whether high-fat or low fat. (*Id.*)

Applicant's studies were also the subject of a Dr. Lammintausta's Declaration. That Declaration also averred important indicia of nonobviousness consistent with the data provided in Applicant's specification.

The Declaration indicated that an improvement of ospemifene bioavailability with food has significant, practical consequences. (Declaration at ¶28.) That effect improves bioavailability 2-3 fold. (*Id.*) That benefit is particularly advantageous in the context of regulation directing that patients consume the lowest safe and effective dose for non-fatal disorders, such as dyspareunia. (*Id.*) The Declaration also provided information demonstrating that bile acids secreted after food consumption are responsible for the increase in ospemifene absorption. (*Id.* at ¶29.) This particular finding contrasts with Anttila which reported the opposite effect, namely a decrease in initial absorption and an overall absorption that remains the same when toremifene is consumed with food. (*Compare id.* with Anttila at Conclusion.)

Information provided by Applicant in the specification of the present application and information in Dr. Lammintausta's Declaration provide evidence of the surprising improvement in bioavailability of ospemifene when consumed with food. This evidence supports patentability of the pending claims. The related evidence of unexpected results must be considered by the Examiner as recognized by the MPEP: "A prima

facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties." (M.P.E.P. 2144.09(VII) *citing In re Papesch*, 315 F.2d 381, (CCPA 1963).)

The Office Action fails to acknowledge the nature and magnitude of the improvement identified by Applicant. (Office Action at p. 9 and p. 17.) Instead, the Office Action repeats the underlying rejection. It also does not acknowledge or address the statements in the Guidance document that the "relative direction and magnitude of food effects on formulation" are "difficult, if not impossible, to predict without conducting a fed [bioequivalence] study." (Guidance document at p. last ¶.)

The results reported in Applicant's specification and information provided in Dr. Lammintausta's Declaration demonstrate the nonobviousness of the claimed invention.

Applicant notes that at the end of the Office Action, the Examiner selectively addresses points made in the Lammintausta Declaration. Specifically, the Examiner states that "there is no showing in comparison how toremifene acts under the same condition." (Office Action at p. 19, 1st ¶.) Moreover, the Examiner adds, "The reliance that food has no effect on Anttila's drug toremifene is found not persuasive because a side by side comparison wherein Anttila's drug toremifene is administered the same way as that claimed and the results compared has not been done. (*Id.*)

As described above, Studies A and B described in Applicant's specification are consistent with the method reported in Anttila. Applicant's studies and the study reported by Anttila used healthy male subjects. (*Compare* Application at ¶29 and Anttila at Methodology, 1st ¶.) Applicant's Study A compared ospemifene bioavailability taken during a fasting state to ospemifene bioavailability taken with a high-fat breakfast (Application at ¶29.) Similarly, Anttila compared ospemifene bioavailability taken during a fasting state to ospemifene bioavailability taken with a high-fat breakfast. (Anttila Methodology at 2nd ¶.) The high-fat breakfast of the two studies consisted of: two eggs fried in butter, two strips of bacon, 60 g of hash brown potatoes, two slices of toast with butter, and 240 ml of whole milk. (*Compare* Application at ¶30 and Anttila Methodology at 2nd ¶.)

In both studies, 60 g of the respective drug was administered to test subjects. (*Compare* Application at ¶36 and Anttila Methodology at 2nd ¶.) Bloods samples were measured for the amount of the respective drug product and a major metabolite. (*Compare* Application at ¶36 and Anttila Methodology at 3rd ¶.) The blood concentrations of the respective drugs and their metabolites were plotted and assessed. (*Compare* Application at Figures 1-3 and Anttila Results Figures 1 and 2.)

The conclusions reported in Anttila indicate, "the extent of absorption is the same under fed and fasted condition . . ." In contrast, Applicant reported a 2-3 fold improvement in bioavailability of ospemifene. (Lammintausta Declaration at ¶28; Application at Figures 1-3; see also Application at ¶44.)

Applicant hopes that in detailing this comparison, the Examiner will reconsider the position outlined in the Office Action and recognize that Applicant, in fact, has provided a side by side comparison of the results of administration of Anttila's drug toremifene and the claimed drug ospemifene. Applicant respectfully submits, therefore that an unexpected improvement in bioavailability was observed for ospemifene that was not observed for toremifene. These surprising results support a finding of the nonobviousness of the claims.

VI. CONCLUSION

In view of the above remarks, Applicant respectfully submits that the claims are in condition for allowance. A prompt notice to that effect is earnestly solicited.

Respectfully submitted,

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